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Description of Patients With Squamous Cell Carcinoma in the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study

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BACKGROUND. The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS) accumulated information regarding conventional and liquid-based Papanicolaou (Pap) cytology, 2 kinds of human papillomavirus (HPV) DNA testing, cervicography, and colposcopically directed biopsy. The prevalence of squamous cell carcinoma in these women, the efficacy of tests, and the time to detection were reviewed.

METHODS. The ALTS data base was reviewed for all women with invasive carcinoma. All results of colposcopy, HPV testing, cytology, biopsies, and cervigrams were reviewed for all women in the ALTS trial who were diagnosed with squamous cell carcinoma.

RESULTS. There were 7 diagnoses of invasive cancer (all squamous cell) during the 2 years of the ALTS trial. Although the enrollment studies isolated many high-grade lesions, none of those results were diagnostic of the underlying carcinoma.

CONCLUSIONS. The prevalence of squamous cell carcinoma in the setting of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion cytology interpretation appears to be low (approximately 1 per 1000 women in the ALTS trial). Many of the carcinomas were not visible on the ectocervix by cervicography or colposcopy, which may explain in part the paucity of atypical cells detected on the Pap tests and the finding that the presenting cytology, although abnormal, was never diagnostic of cancer. HPV DNA tests were

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positive in all 7 cancers. Type-specific testing identified HPV type 16 in 6 of 7 cancers and HPV type 18 in 1 of 7 cancers. ***Cancer (Cancer Cytopathol)* 2006;108:212–21.** *© 2006 American Cancer Society.*

KEYWORDS: squamous cell carcinoma, cervical cancer, Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion.

Routine screening for cervical cancer has led to the earlier detection of invasive carcinomas and increased treatment of precursor lesions, such as high-grade cervical intraepithelial neoplasia (CIN). These efforts are responsible in part for the decrease in the incidence of and mortality from cervical cancer in the U.S.[1] Despite this, the Papanicolaou (Pap) test (Pap smear or liquid-based cytology) is imperfect, and the classification of atypical cells can be problematic. Some women who receive routine Pap tests will develop squamous cell carcinoma with only a history of mildly atypical cells and without an antecedent high-grade squamous intraepithelial lesion (HSIL) cytologic interpretation. The current study was undertaken to review the 7 patients in the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS) who had invasive cancer. Because nearly all of the carcinomas were found within the first year of the study and cervical cancer typically develops over a longer time course, it is assumed that these women had cancer at the time of referral. In the current study, we summarized the ALTS cytopathology, pathology, cervicography, human papillomavirus (HPV) status, colposcopic impression, and clinical course for these 7 women to gain a better understanding of the limitations of screening and triage tests to detect occult cancers.

MATERIALS AND METHODS

The ALTS trial was a randomized, 2-year trial conducted by the National Cancer Institute (National Institutes of Heath, Rockville, MD), which compared 3 different management protocols for women with atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL). In all, 5060 women were enrolled in the study between 1997 and 1998, including 3488 women with ASCUS and 1572 women with LSIL, and were randomized to undergo either immediate colposcopy, HPV testing, or conservative management (repeat cytology), as described previously.[2–4] Each woman answered a questionnaire that investigated in detail her demographics, medical history, and sexual history. The initial referral Pap test from the community that showed either ASCUS or LSIL was followed by an enrollment liquid-based cytology (ThinPrep; Cytyc Corporation, Boxborough, MA). Enrollment was considered Time 0 for the study. At each of 5 semiannual visits, cytology was repeated, and HPV status was evaluated. However, HPV test results were masked to clinicians, with the exception of enrollment results for patients in the HPV triage arm. Hybrid Capture 2 (HC2) testing with Probe Set B (Digene Corporation, Gaithersburg, MD) was performed by using a 4-mL aliquot of the residual PreservCyt (Cytyc Corporation) liquid. PGMY09/11 L1 consensus primer polymerase chain reaction (PCR) was performed from a cocollected Dacron swab specimen that was placed into specimen transport medium (Digene Corporation).[5–9] HPV type 16 (HPV-16), HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, and HPV-68 were considered high risk, oncogenic types. All women, regardless of their randomization assignment, had cytology, HPV testing, and cervigrams every 6 months for 2 years.

Referral, enrollment, and subsequent Pap tests and biopsy histology were reviewed by a quality control pathology (QCP) group. The clinical management was based on cytologic interpretations and histologic diagnoses of a clinical center pathologist (CCP); however, if the CCP interpretation would not have triggered clinical action and the QCP diagnosis was CIN3 or cancer, then a safety-net alert was sent to the clinician.

The ALTS data base was queried for all new diagnoses of invasive carcinoma during the 2 year trial. All cytology and histology specimens were reviewed and correlated with colposcopic findings, cervicography results, and time to detection.

RESULTS

Seven of 5060 women (0.14%) had squamous cell carcinoma, including 3 with microinvasion and 4 with ≥5 mm of invasion (International Federation of Gynecology and Obstetrics clinical Stage IB). These patients and their clinical course are described and summarized below and in Tables 1 and 2. Pap tests and biopsy results are shown with the CCP interpretation first. When the QCP interpretation differed, it is noted in parentheses. Test results are summarized chrono-

TABLE 1
Patient Medical Histories

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age, y	36	27	26	41	39	43	23
No. of Pap tests in past 5 years	0	5	15*	5	2	1	5
Abnormal Pap	No	No	No	Yes (distant)	No	No	Yes (distant)
Age at first intercourse, y	17	18	15	15	11	17	17
No. of sexual partners	3	4	10	10-20	≥95	10-20	5
Smoking history, y	7	10	11	None	26	22	None
STDs	T	None	G	CL, G, T	None	CL	None
GXPX	G0P0	G2P2	G2P2	G8P5	G3P2	G1P0	G1P0
BC method	Condoms	Norplant	OBC/Inj	Inj/condom	Condom	Condom	OBC, condom
Abnormal bleeding	No	DC	None	Bloody DC	None	None	None

Pap indicates Papanicolaou; STDs: sexually transmitted diseases; T: Trichimonas; G: gonorrhea; CL: chlamydia; BC: birth control; OBC: oral birth control pills; Inj: injection; DC: discharge; GXPX: gravida para.
* Results were tabulated from patient questionnaires.

logically according to the dates of specimen collection. However, it is important to emphasize that clinicians were masked to all HPV results (except HC2 results from enrollment in the HPV triage arm) and to all cervigram findings until the final exit visit. In addition, PCR testing was not performed until after the conclusion of the trial; therefore, HPV type-specific results were never available to clinicians. Results from procedures that were performed at a visit but that were not available to the clinician at the time of evaluation are shown in brackets in the text below.

Patient 1 was a woman age 36 years who had not had a Pap test in 19 years. The referral Pap smear was interpreted as LSIL (ASCUS by the QCP). She was randomized to the conservative-management arm, and her enrollment ThinPrep results were interpreted as reactive cellular changes by the CCP; therefore, she was not referred for colposcopy. [HC2 was positive, with HPV-16 detected by PCR, and a cervigram was compatible with a low-grade lesion.] Her 6-month follow-up Pap test demonstrated ASCUS. [Masked HPV testing demonstrated persistent positive HC2 results, with HPV-16 detected by PCR.] At her 12-month visit, pelvic examination revealed abnormal appearance of the cervix that triggered referral for colposcopy. The colposcopist's impression was carcinoma; however, a biopsy demonstrated only CIN1 (Fig. 1). Six months later, 18 months after enrollment, colposcopy was repeated (secondary to the 6-month colposcopic impression) and was suspicious for a high-grade lesion; concurrent biopsy showed invasive squamous cell carcinoma (Fig. 1). The patient underwent a hysterectomy with lymph node dissection, which demonstrated a circumferential invasive squamous cell carcinoma that extended into the lower uterine segment and measured 1.5 cm in greatest depth. Twenty-five lymph nodes were free of metastatic disease.

Patient 2 was a woman age 27 years who routinely obtained annual Pap tests; none had been abnormal. Her referral Pap smear was interpreted as LSIL; however, her ThinPrep cytology results at enrollment were interpreted as HSIL. HC2 was positive. [HPV-16 was detected by PCR, and a cervigram was compatible with a high-grade lesion (Fig. 2).] She was randomized to the HPV arm of the study and underwent colposcopy because of her enrollment Pap test and the HPV results. The colposcopist's impression was high-grade dysplasia, and a biopsy demonstrated CIN3. A follow-up excision specimen contained microinvasive squamous cell carcinoma. The patient opted for a hysterectomy, which demonstrated CIN3 but no residual invasive carcinoma.

Patient 3 was a woman age 26 years who routinely obtained annual Pap smears, all reportedly were normal. Her referral Pap smear was interpreted as LSIL (HSIL by the QCP), and she was randomized to the immediate-colposcopy arm. The concurrent enrollment ThinPrep results were interpreted as ASCUS. [The cervigram was consistent with a high-grade lesion, and HC2 was positive, with HPV-11, HPV-16, and HPV-45 detected by PCR.] The colposcopic impression was also high grade, and the biopsies were diagnosed as CIN3 (Fig. 2). A loop electrosurgical excision procedure (LEEP) revealed microinvasive squamous cell carcinoma. A subsequent simple hysterectomy (slides not available for our review) showed CIN3. The CCP identified a potential second focus of microinvasive squamous cell carcinoma, but the QCP interpreted it as CIN3.

Patient 4 was a woman age 41 years who had 2 Pap smears in the previous 5 years. She had a remote history of an abnormal Pap smear and a biopsy (pathology results unknown) and currently was being treated for gonorrhea and Trichomonas. She was re-

TABLE 2
Screening and Treatment Course

Screening/Treatment	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Randomized arm	CM	HPV	IC	IC	IC	CM	CM
Referral Pap test*	LSIL (ASCUS)	LSIL (LSIL)	LSIL (HSIL)	LSIL (HSIL)	ASCUS (HSIL)	LSIL (LSIL)	ASCUS (reactive)
Zero mo							
Enrollment Pap test*	Reactive (reactive)	HSIL (HSIL)	LSIL (ASCUS)	HSIL (HSIL)	ASCUS (reactive)	HSIL (HSIL)	HSIL (HSIL)
HC2	Positive	Positive	Positive	Positive	Positive	Positive	Positive
HPV PCR	HPV-16	HPV-16	HPV-11, -16, -45	HPV-16	HPV-16, -18	HPV-18, -42	HPV-16
Cervigram†	P1	P2	P2	Negative	Negative	Atypical	
Colposcopy		HG	HG	LG	Normal	LG	HG
Biopsy		CIN3	CIN3	ND	ND	CIN2	CIN3
Excision		Microinv SCCa	Microinv SCCa	Inv SCCa (off study)		Microinv SCCa	CIN3
6 mo							
Repeat Pap test*	ASCUS (ASCUS)				Normal (ASCUS)	Reactive (reactive)	HSIL (HSIL)
HC2	Positive				Positive	Negative	Positive
HPV PCR	HPV 16				HPV-16, -18	HPV-42	HPV-16
Cervigram†	P1				Negative	Negative	P1
Colposcopy							Patient refused
Biopsy						Reactive	Metaplasia
Excision							Inv SCCa
12 mo							
Repeat Pap test*	ASCUS				Reactive (negative)	Negative (reactive)	
HC2	Positive				Positive	Negative	
HPV PCR	HPV-59				HPV-16, -18	HPV-42	
Cervigram†					Negative	Negative	
Colposcopy	Cancer				Insuff		
Biopsy	CIN1				CIN3		
Excision					Inv SCCa		
18 mo							
HC2	Positive					Negative	
HPV PCR	HPV-16					Negative	
Repeat Pap test*	ASC (LSIL)					Negative (reactive)	
Cervigram†	P3					Negative	
Colposcopy	HG						
Biopsy	Inv SCCa						
24 Months							
HC2						Negative	
HPV PCR						Negative	
Pap test							
Cervigram†						Negative	
Colposcopy						Negative	
Excision						Normal	
Hysterectomy	Yes	Yes	Yes	Unknown	Unknown	No	Unknown

CM: conservative management, HPV: human papillomavirus screening; IC: immediate colposcopy; Pap: Papanicolaou; LSIL: low-grade squamous intraepithelial lesion; ASCUS: atypical squamous cells of undetermined significance; HSIL: high-grade squamous intraepithelial lesion; HC2: Hybrid Capture 2; PCR: polymerase chain reaction; HG: high-grade; LG: low-grade; CIN: cervical intraepithelial neoplasia; ND: not done; Microinv; microinvasive; SCCa: squamous cell carcinoma; Inv: invasive; Insuff: insufficient.

* The clinical center pathologist interpretation is shown first, and the quality control pathologist interpretation is indicated in parenthesis.

† Cervigram interpretations: X, not performed; atypical, mild abnormality but colposcopy is not recommended; P1, low-grade lesion; P2, high-grade lesion; P3, carcinoma.

ferred for an LSIL Pap smear (which was interpreted as HSIL-CIN3 by the QCP), and her enrollment ThinPrep results were interpreted as HSIL by both the CCP and the QCP. The patient was randomized to the immediate-colposcopy arm of the study but would have been seen by a colposcopist regardless of the management arm because of the QCP diagnosis on her referral Pap smear and the enrollment ThinPrep interpretations. [HC2 was positive, with HPV-16 and HPV-45 detected by PCR; and a cervigram was negative (Fig. 2).] The colposcopic impression was low grade. Biopsies that were performed off study 7 months later showed invasive carcinoma. Subsequent treatment was not known.

Patient 5 was a woman age 39 years who had 2 normal Pap smears over the previous 5 years. Her referral Pap smear was interpreted as ASCUS (HSIL by the QCP). She was randomized to immediate colposcopy, which was normal, and no biopsy was taken. [A cervigram also was negative (Fig. 3).] The enrollment ThinPrep results were interpreted as LSIL (reactive by the QCP). [HC2 was positive, with HPV-16, HPV-18, and HPV-51 detected by PCR.] A repeat ThinPrep at 6 months was interpreted as negative (ASCUS by the QCP). [HC2 remained positive, with HPV-16 and HPV-18 detected by PCR.] One year after enrollment, the ThinPrep results were interpreted as negative. [However, her HC2 results remained positive, with HPV-16 and HPV-18 detected by PCR.] A safety-net colposcopy was triggered by the QCP review of the referral Pap test. The colposcopy was considered suboptimal, and a biopsy demonstrated CIN3. A follow-up LEEP demonstrated invasive squamous cell carcinoma. Further treatment was not known.

Patient 6 was a woman age 43 years who had 1 Pap smear in the previous 5 years. She had a remote history of an abnormal Pap smear, which had been monitored with a follow-up Pap smear. Her referral Pap smear was interpreted as LSIL. She was randomized to conservative management. Her enrollment ThinPrep results were interpreted as HSIL. [HC2 was positive, with HPV-18 and HPV-42 detected by PCR; and a cervigram was interpreted as atypical.] She was referred for colposcopy because of the HSIL cytology: It was suspicious for low-grade dysplasia, and a biopsy showed CIN2. A subsequent LEEP revealed microinvasive squamous cell carcinoma. Three months later, a Pap test was interpreted as negative. [HC2 was negative, with HPV-42 detected by PCR.] A reexcision 4 months later demonstrated reactive changes only. All subsequent Pap tests, HC2, and colposcopic examinations were negative.

Patient 7 was a woman age 23 years who had received annual Pap tests with no history of abnormal cytology. The referral Pap smear was interpreted as ASCUS (reactive by the QCP), but the enrollment ThinPrep results were interpreted as HSIL. She was randomized to conservative management and was referred for colposcopy because of the HSIL Pap interpretation. No cervigram was obtained. The colposcopic impression was high-grade dysplasia. [HC2 was positive, with HPV-16 detected by PCR.] A biopsy and subsequent LEEP biopsy showed CIN3. A biopsy at her 5-month follow-up visit demonstrated squamous metaplasia. However, a concurrent ThinPrep was interpreted as HSIL. [HC2 was positive, with HPV-16 detected by PCR.] A second excision revealed squamous cell carcinoma. Subsequent treatment was not known.

Summary of Patients and Clinical Course

These women with screen-detected lesions (Tables 1 and 2) were younger than the average age of women with cervical cancer in the U.S.[10] However, as a group, they demonstrated some of the typical characteristics of patients with cervical cancer, with histories of early age at first intercourse, smoking, oral contraceptive use, and other sexually transmitted infections.[11]

The clinical data are summarized in Table 2. Six of 7 women had immediate referral for colposcopy based on their randomization arm and their enrollment triage test results, including 3 of 3 women in the immediate-colposcopy arm, 1 of 1 woman in the HPV arm, and 2 of 3 women in the conservative-management arm.

Of the 7 referral Pap tests for ASCUS or LSIL, 3 were upgraded to HSIL by the QCP, 1 was downgraded from LSIL to ASCUS, and 1 was downgraded to reactive. At enrollment, the Pap tests from 4 of the women were interpreted as HSIL by both the CCP and the QCP. The LSIL and ASCUS CCP interpretations on 2 other women were downgraded to ASCUS and reactive, respectively, by the QCP. The Pap test from Patient 7 was interpreted as reactive by both the CCP and the QCP. Overall, a diagnosis of HSIL was made in 6 of 7 of women 1 of their first 2 Pap tests (referral or enrollment) by either the primary or QCP.

Enrollment HC2 HPV testing was positive in all 7

FIGURE 1. Patient 1 underwent a (A) 12-month ThinPrep interpretation of atypical cells of undetermined significance (ASCUS) and (B) a colposcopic biopsy, which demonstrated cervical intraepithelial neoplasia 1. Because of a more worrisome colposcopic impression, the patient underwent a repeat colposcopic examination at 18 months with (C) a ThinPrep test, which was interpreted as ASCUS (low-grade squamous intraepithelial lesion by the quality control pathology group), and (D) a biopsy, which demonstrated invasive squamous cell carcinoma.

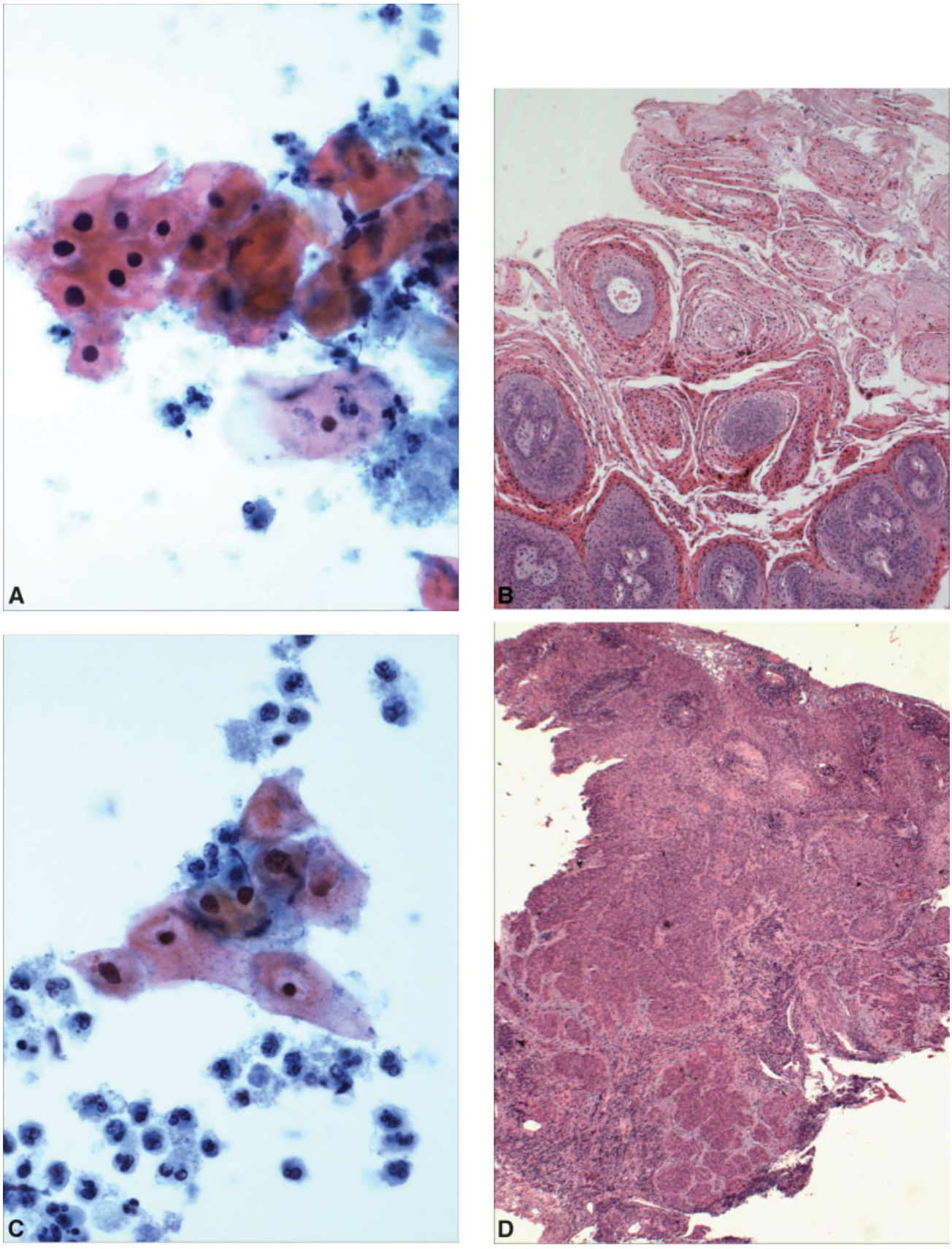


FIGURE 1.

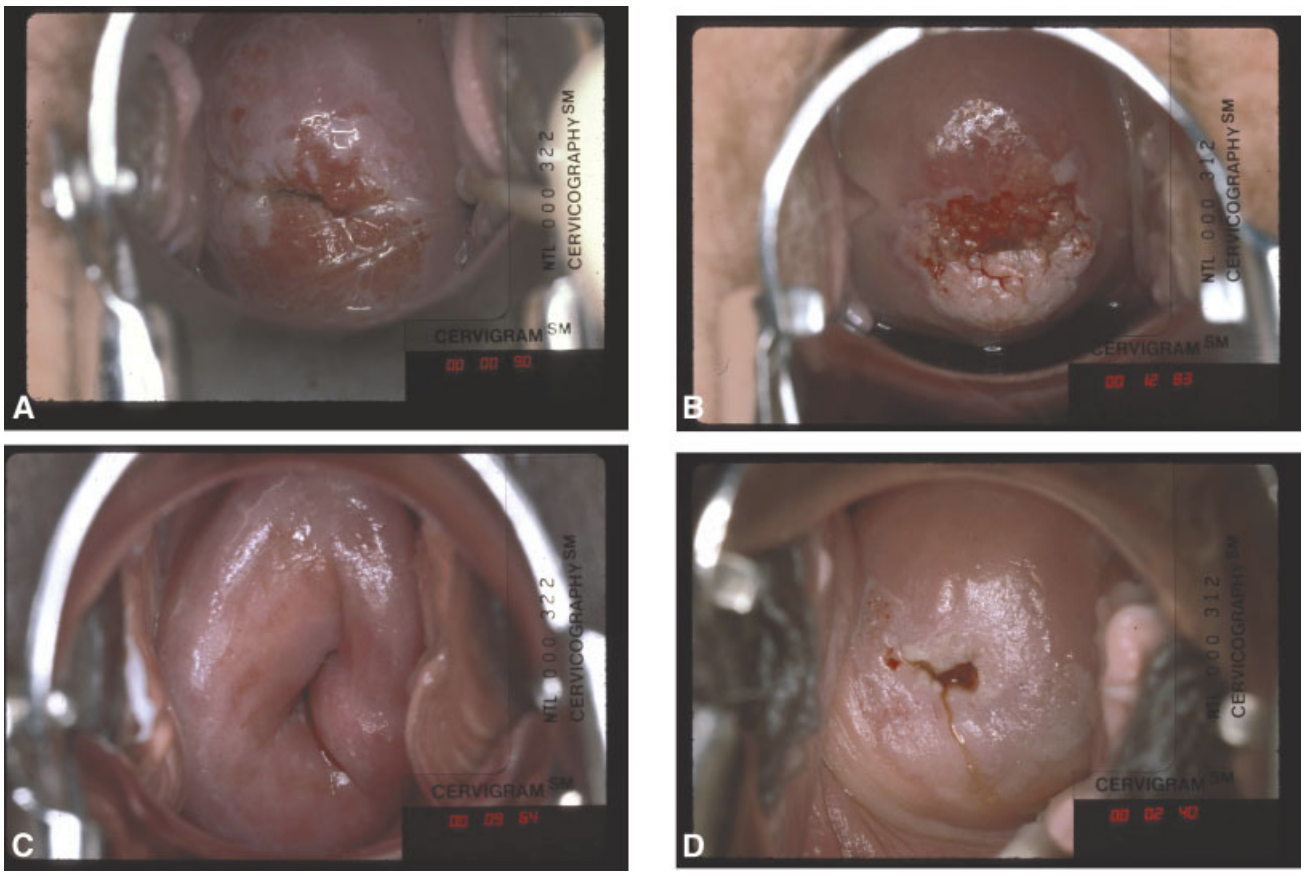


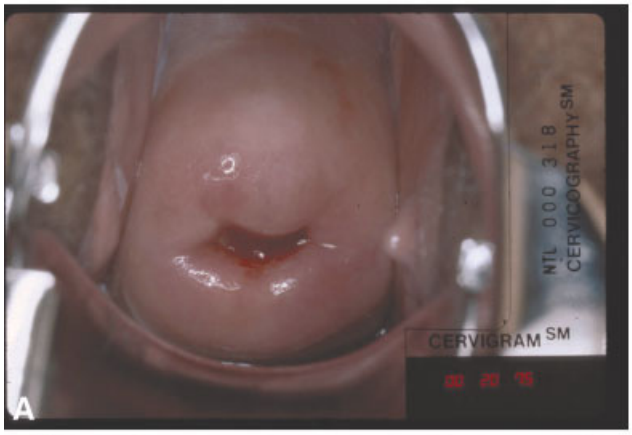
FIGURE 2. Of the 6 enrollment cervigrams, 2 demonstrated high-grade changes (P2) (Patient 2 in Panel A, Patient 3 in Panel B), and 2 cervigrams were negative for enrollment abnormality (Patient 4 in Panel C, Patient 5 [see Fig. 1]). The entrance cervigram for Patient 1 (D) demonstrated low-grade changes, and the cervigram for Patient 6 demonstrated mild abnormalities (not shown).

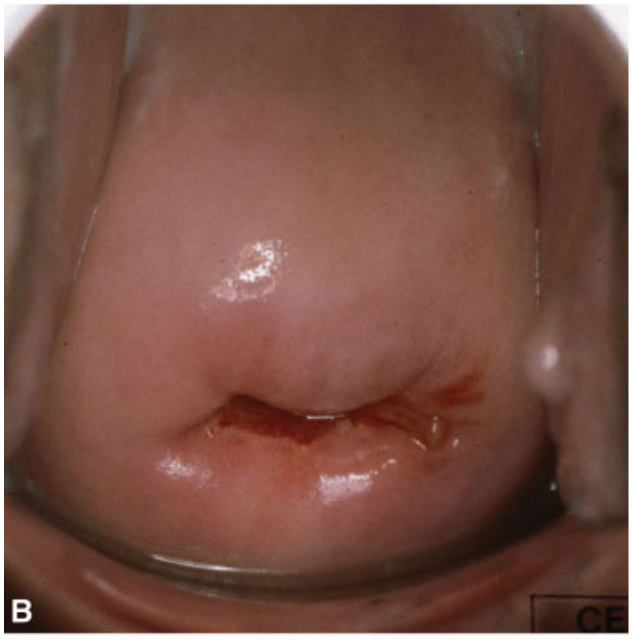
patients: PCR identified HPV-16 in 6 women and HPV-18 in 1 woman. The patients with the longest time to detection (Patients 1, 5, and 7) had persistent HPV detected by HC2. Patient 6 underwent LEEP biopsy, and all of her subsequent HPV HC2 tests were negative, correlating to negative Pap tests and subsequent biopsies.

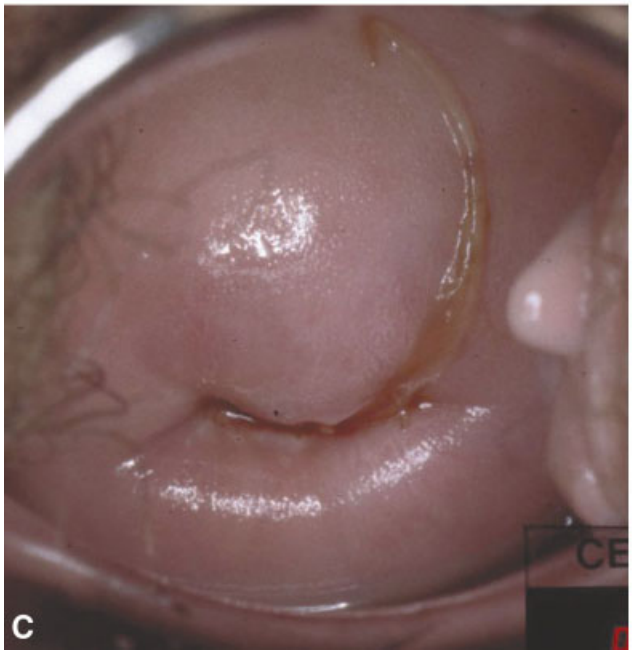
Six of 7 women had enrollment cervigrams that were categorized as follows: negative in 2 women, atypical in 1 woman, low grade in 1 woman, and high grade in 2 women. No cervigram results were compatible with carcinoma. Six women underwent colposcopy at enrollment, and the impressions were negative in 1 woman, low grade in 2 women, and high grade in 3 women. Colposcopy *and* cervicography were compatible with high-grade lesions in 2 of 5 women who had both at enrollment. The third woman with a colposcopic impression of high-grade dysplasia (Patient 7) did not undergo an enrollment cervigram. No cervigram showed a lesion more worrisome than the colposcopic impression.

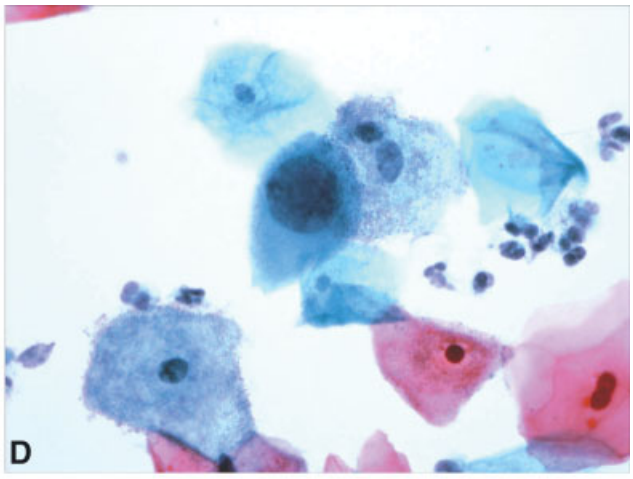
Four women underwent biopsies at the time of their enrollment colposcopy, and all 4 women had CIN2 or CIN3 diagnosed by the CCP. None demonstrated the invasive carcinoma that was found on subsequent excision procedures, including 2 women who had International Federation of Gynecology and Obstetrics (FIGO) Stage IIB invasive disease (Patients 4 and 7; see Tables 1 and 2). However, 4 of the carcinomas were found on the LEEP that was triggered by enrollment information. Pa-

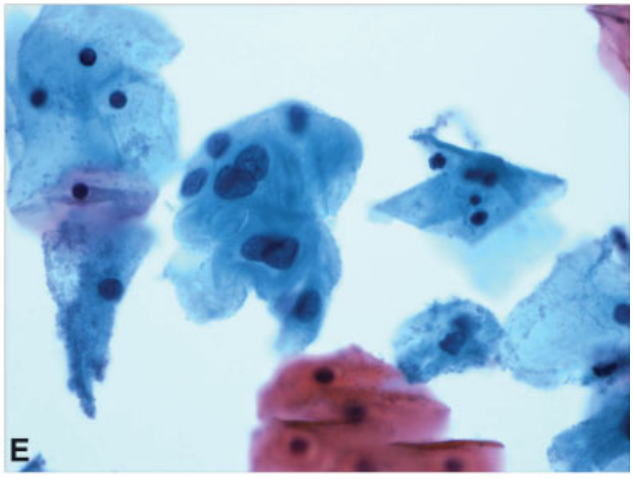
FIGURE 3. Cervigrams for Patient 5 at (A) the time of enrollment, (B) at 6 months, and (C) at 12 months all were normal. The concurrent ThinPrep tests were interpreted as (D) atypical cells of undetermined significance (ASCUS) by the clinical center pathologist (CCP) and downgraded to reactive by the quality control pathologist (QCP) at the time of enrollment, (E) negative by the CCP and upgraded to ASCUS by the QCP at 6 months, and (F) reactive at 12 months. A biopsy performed at 12 months demonstrated cervical intraepithelial neoplasia 3 and a subsequent loop electrosurgical excision procedure revealed invasive squamous cell carcinoma.











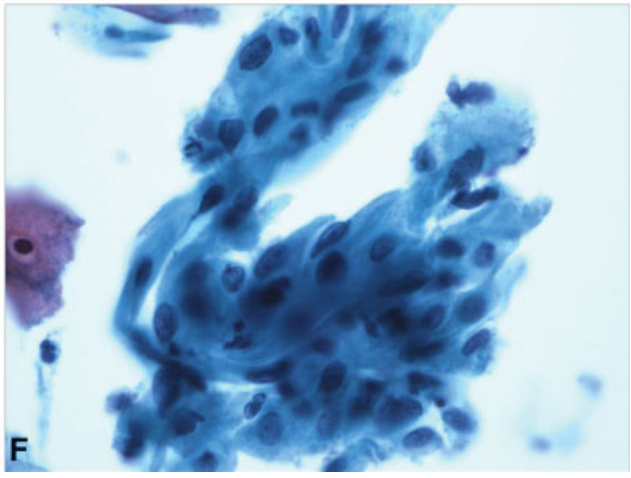


FIGURE 3.

tients 1 and 5 had the seemingly most delayed diagnoses (18 months and 12 months, respectively), although carcinoma was suspected in Patient 1 on colposcopy at 12 months, but only CIN1 was found on biopsy. It is noteworthy that no patient had unequivocal evidence of underlying cancer or CIN3 on all diagnostic modalities, despite our presumption that the disease already was prevalent at enrollment.

DISCUSSION

The current prevalence of cervical dysplasias, the significance of oncogenic HPV and its utility in the management of various Pap test interpretations, and correlations of cervigrams and colposcopy are emerging[12-14] as data from the ALTS trial and other large studies are evaluated. Within ALTS, 542 of 5060 women (10.1%) had CIN3, and 7 women (0.14%) had invasive carcinoma. Because most of the women were diagnosed with invasive carcinoma within the first year of enrollment, it is assumed that the carcinoma was present but undetected at the time of referral. Four of the 7 women with carcinoma had their disease detected at enrollment, and a fifth woman had her disease detected at the 6-month visit.

In the current analysis, a fraction of the initial "misses" of carcinoma on the referral Pap tests were a result of Pap test interpretation variability. Of the 7 referral Pap tests, the QCP upgraded 3 ASCUS or LSIL interpretations to HSIL. Although, retrospectively, these upgrades were appropriate, it is important to note that the QCP also downgraded some of the CCP interpretations (1 ASCUS interpretation was downgraded to reactive, and 1 LSIL interpretation was downgraded to ASCUS). There was more agreement on the enrollment ThinPrep results, with 4 concordant HSIL interpretations. The QCP downgraded 1 LSIL interpretation to ASCUS and 1 ASCUS interpretation to reactive. The interpretive variation of cervical cytology, as observed in the ALTS trial between the CCP and the QCP, has been well documented.[15] It is noteworthy that the numbers of upgrades and downgrades by the QCP essentially were equal, suggesting that most of the variation is caused by the problems of interpreting a limited number of mildly abnormal cells.

Although some studies have shown that cervicography increases the sensitivity of cervical screening in detecting high-grade lesions, the current study exemplifies how challenging the detection of carcinoma can be in some women. Six of the women had cervigrams at their enrollment visit. Only 2 women had results that were suspicious for high-grade lesion (they also had concurrent colposcopy results that were compatible with high-grade lesion), and none had results that were compatible with carcinoma. The cervigram and colposcopic impressions mostly were similar, with 2 interpretations of suspected CIN3 in both modalities (see Table 2). The 2 patients who had the most delayed diagnoses, Patients 1 and 5, had P1 (low-grade) or normal cervigrams at their initial and 6-month evaluations. Although none of the 6 enrollment colposcopies identified carcinoma, 3 were compatible with high-grade lesions (Patients 2, 3, and 7). Although the colposcopic biopsies identified CIN2 and CIN3, prompting further treatment and ultimate correct diagnoses, none demonstrated the invasive carcinoma that was found on the subsequent excision.

The most consistent result in these 7 women was a positive HPV result by HC2, which was persistent in the women who had >1 HPV test prior to treatment. PCR was positive for HPV16 in 6 women and HPV18 in 1 woman: These HPV types may merit separate identification in testing.[16]

In the current cohort, the prevalence of squamous cell carcinoma in women coming to clinical attention because of equivocal or mildly atypical cervical cytology was approximately 1 per 1000 women. It is not surprising that the incidence of cervical carcinoma in this select population was greater than what is found in the general population of women ages 20 years to 40 years (range, from 0.05 per 1000 to 0.15 per 1000).[10] In this study, the prevalence of cancer among women with ASCUS or LSIL *and* with oncogenic HPV was 2 per 1000 women. These occult cancers, which are detected subsequent to an initial screening result of ASCUS or LSIL cytology, most likely are not representative of cervical cancers generally, but these results do highlight the limitations of morphologic and visual assessment to diagnose some cancers, perhaps because of lesion location or sampling issues.

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